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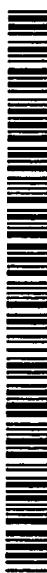
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(54) Title: REDUCTION OF HAIR GROWTH

(57) Abstract: Mammalian hair growth is reduced by applying to the skin a composition that increases cellular ceramide levels.

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### REDUCTION OF HAIR GROWTH

The invention relates to reducing hair growth in mammals, particularly for cosmetic purposes.

A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts, and can leave a perception of an increase in the rate of hair regrowth. Shaving also can leave an undesirable stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the rate and character of hair growth can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase, ornithine decarboxylase, S-adenosylmethionine decarboxylase, gammaglutamyl transpeptidase, and transglutaminase. See, for example, Breuer et al., U.S. Pat. No. 4,885,289; Shander, U.S. Pat. No. 4,720,489; Ahluwalia, U.S. Pat. No. 5,095,007; Ahluwalia et al., U.S. Pat. No. 5,096,911; and Shander et al., U.S. Pat. No. 5,132,293.

Ceramide is a naturally occurring sphingolipid metabolite present in skin and other tissues both intra- and extra-cellularly. Biosynthesis of ceramide in cells generally starts by the condensation of the amino acid serine and palmitoyl-CoA resulting in the formation of 3-ketodihydrosphingosine, which is subsequently reduced to dihydrosphingosine. The amide linkage of fatty acyl groups to dihydrosphingosine forms dihydroceramide. The dihydroceramide is

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converted to ceramide by the introduction of a trans-4,5-double bond. Once formed, ceramide acts as a precursor for the synthesis of other complex sphingolipids such as galactosylceramide, glucosylceramide, and acyl ceramide. Most glycosphingolipids are synthesized from ceramide via glucosylceramide, the 5 formation of which is catalyzed by glucosylceramide synthase.

Ceramide is also formed in cells by pathways of complex glycosphingolipid catabolism. For example, the breakdown of sphingomyelin through the action of sphingomyelinases results in the formation of ceramide. Another set of enzymes that may regulate cellular ceramide levels are ceramidases, 10 which break down ceramide to sphingosine.

The invention features reducing unwanted mammalian (including human) hair growth -- particularly androgen-stimulated hair growth -- by increasing cellular ceramide levels. Cellular ceramide levels may be increased, for example, by applying to the skin a composition including (1) an inhibitor of glucosylceramide 15 synthase, (2) an inhibitor of ceramidase; (3) ceramide (N-acyl-trans-D-erythro-2-amino-4-octadecene-1,3-diol); (4) a ceramide analog; and/or (5) an inducer of sphingomylinase. A ceramide analog is a chemical derivative of the ceramide molecule that either behaves as ceramide or is degraded in cells to ceramide. The unwanted hair growth which is reduced may be normal hair growth, or hair growth 20 that results from an abnormal or diseased condition. For purposes of this application, glucosylceramide synthase includes glucosyl ceramide transferase.

Other features and advantages of the invention may be apparent from the description of the preferred embodiments thereof, and from the claims.

A preferred composition includes at least one compound that 25 increases cellular ceramide levels when applied topically in a cosmetically and/or dermatologically acceptable vehicle. The composition may be a solid, semi-solid, or liquid. The composition may be, for example, a cosmetic and dermatologic product in the form of an, for example, ointment, lotion, foam, cream, gel, or hydroalcoholic solution. The composition may also be in the form of a shaving 30 preparation or an aftershave. The vehicle itself can be inert or it can possess cosmetic, physiological and/or pharmaceutical benefits of its own.

Examples of inhibitors of glucosylceramide synthase: 1-phenyl-2-

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decanoyleamino-3-morpholino-1-propanol (PDMP); 1-phenyl-2-hexadecanoylamino-3-morpholino-1-propanol (PPMP); 1-phenyl-2-hexadecanoylamino-3-pyrrolidino-1-propanol (PPPP); 1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol (P4); D-threo-4'-hydroxy-P4; D-threo-3',4'-methylenedioxyphenyl-P4;

5 D-threo-trimethylenedioxyphenyl-P4; D-threo-3',4'-ethylenedioxyphenyl-P4; N-butyldeoxynojirimycin (NBDN); and N-(5-adamantane)-1-ylmethoxy)pentyl)-deoxy norjirimycin. See Rani et al., J. Biol. Chem. 270: 2859-2867, 1995; Olshefski and Ladisch, J. Neurochem. 70: 467-472, 1998; Lee et al., J. Biol. Chem. 274: 14662-14669, 1999; Neises et al., Biol. Cell 89: 123131, 1997; and Platt et al. J.

10 Biol Chem. 269: 8362-8365, 1994.

Examples of inhibitors of ceramidase include the following:

D-erythro-2-(N-myristoylamino)-1-phenyl-1-propanol (D-erythro-MAPP); N-oleoyl ethanolamine; and (1S,2R)-(+)-phenylpropanolamine. See Spinedi et al., Biochem. Biophys. Res. Commun. 255: 456-459, 1999; Bielawska et al., J. Biol. Chem. 271: 15 12646-12654, 1996.

Examples of ceramide analogs include the following:

N-acetylsphingosine (C<sub>2</sub>-ceramide); N-hexanoylsphingosine (C<sub>6</sub>-ceramide); N-octanoylsphingosine (C<sub>8</sub>-ceramide); N-octanoyl-DL-erythro dihydrosphingosine; N-octyl-D-erythrosphingosine; and N-thioacetylsphingosine; and 4-dodecanoyl-20 amino-decan-5-ol. See Park et al., Exp. Mol. Med. 31: 142-150, 1999; Irie and Hirabayashi, J. Neurosci. Res., 54: 475-485, 1998; Karasavvas et al., Eur. J. Biochem. 236: 729-737, 1996; and Bektas et al., Exp. Dermatol. 7: 342-249, 1998.

The composition may include more than one compound that increases cellular ceramide levels. In addition, the composition may include one or more 25 other types of hair growth reducing agents, such as those described in U.S. Pat. No. 4,885,289; U.S. Pat. No. 4,720,489; U.S. Pat. No. 5,132,293; U.S. Pat. No. 5,096,911; U.S. Pat. No. 5,095,007; U.S. Pat. No. 5,143,925; U.S. Pat. No. 5,328,686; U.S. Pat. No. 5,440,090; U.S. Pat. No. 5,364,885; U.S. Pat. No. 5,411,991; U.S. Pat. No. 5,648,394; U.S. Pat. No. 5,468,476; U.S. Pat. No. 30 5,475,763; U.S. Pat. No. 5,554,608; U.S. Pat. No. 5,674,477; U.S. Pat. No. 5,728,736; U.S. Pat. 5,652,273; WO 94/27586; WO 94/27563; and WO 98/03149, all of which are incorporated herein by reference.

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The concentration of the compound that increases cellular ceramide levels in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight or even more; the reduction of hair growth increases as the amount of compound applied increases per unit area of 5 skin. The maximum amount effectively applied is limited only by the rate at which the compound penetrates the skin. The effective amounts may range, for example, from 10 to 3000 micrograms or more per square centimeter of skin.

Vehicles can be formulated with liquid or solid emollients, solvents, thickeners, humectants and/or powders. Emollients include stearyl alcohol, mink 10 oil, cetyl alcohol, oleyl alcohol, isopropyl laurate, polyethylene glycol, olive oil, petroleum jelly, palmitic acid, oleic acid, and myristyl myristate. Solvents may include ethyl alcohol, isopropanol, acetone, diethylene glycol, ethylene glycol, dimethyl sulfoxide, and dimethyl formamide.

The composition also may include components that enhance the 15 penetration of the compound into the skin and/or to the site of action. Examples of penetration enhancers include urea, polyoxyethylene ethers (e.g., Brij-30 and Laureth-4), 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene, terpenes, cis-fatty acids (e.g., oleic acid, palmitoleic acid), acetone, laurocapram, dimethylsulfoxide, 2-pyrrolidone, oleyl alcohol, glyceryl-3-stearate, propan-2-ol, myristic acid isopropyl 20 ester, and propylene glycol.

The composition also can be formulated to provide a reservoir within or on the surface of the skin to provide for a continual slow release of a compound that increases cellular ceramide levels. The composition also may be formulated to evaporate slowly from the skin, allowing the inhibitor extra time to penetrate the 25 skin.

The following are examples of compositions including a compound that increases cellular ceramide levels.

#### Example 1

Compositions were prepared containing PDMP, PPMP, PPPP, 30 (1S,2R)-(+)-phenylpropanolamine and N-oleoylethanolamine in a vehicle containing water 68%, ethanol 16%, propylene glycol 5%, dipropylene glycol 5%, benzyl alcohol 4%, and propylene carbonate 2%. These compositions were tested for their

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effect on hair growth; the results are provided in Table 1, along with the weight quantities of the relevant compound in the composition.

Example 2

Compositions were prepared containing C<sub>8</sub>-ceramide, C<sub>6</sub>-ceramide and C<sub>2</sub>-ceramide in a vehicle containing water 68%, ethanol 16%, propylene glycol 5%, dipropylene glycol 5%, benzyl alcohol 4%, and propylene carbonate 2%. The compositions were tested for their effect on hair growth; the results are provided in Table 1, along with the weight quantities of the relevant compound in the composition.

10

Example 3

Compositions were prepared including the compounds listed in Example 1 (same weight quantities) in a vehicle containing water 80.84%, glyceryl stearate 4.24%, polyethylene glycol 100-stearate 4.09%, cetearyl alcohol 3.05%, ceteareth-20 2.5%, mineral oil 2.22%, stearyl alcohol 1.67%, and dimethicone 15 0.56%.

Example 4

Compositions were prepared including the compounds listed in Example 2 (same weight quantities) in a vehicle containing water 80.84%, glyceryl stearate 4.24%, polyethylene glycol 100-stearate 4.09%, cetearyl alcohol 3.05%, 20 ceteareth-20 2.5%, mineral oil 2.22%, stearyl alcohol 1.67%, and dimethicone 0.56%.

Optionally, one of the penetration enhancers mentioned previously may be added to a composition. A penetration enhancer could be added at concentrations of, for example, 0.10% to 20% by weight. The preferred 25 concentration is 0.5% to 5% by weight.

The composition should be topically applied to a selected area of the body from which it is desired to reduce hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition also may be used as an adjunct to other 30 methods of hair removal including shaving, waxing, mechanical epilation, chemical depilation, electrolysis and laser-assisted hair removal.

The composition can also be applied to the legs, arms, torso or

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armpits. The composition is particularly suitable for reducing the growth of unwanted hair in women suffering from hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, to achieve a perceived reduction in hair growth. Perception of reduced hair growth 5 could occur as early as 24 hours or 48 hours (for instance, between normal shaving intervals) following use or could take up to, for example, three months. Reduction in hair growth is demonstrated when, for example, the rate of hair growth is slowed, the need for removal is reduced, the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed (i.e., hair mass) is reduced.

10 Golden Syrian Hamster Assay

Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter. These organs produce fine light colored hair typical of the animal pelage found on the body. In response to 15 androgens the flank organs produce dark coarse hair similar to male human beard hair. To evaluate the effectiveness of a composition including a compound that increases cellular ceramide levels, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex) and/or shaved. To one organ of each animal 10  $\mu$ l of vehicle alone once a day is applied, 20 while to the other organ of each animal an equal amount of vehicle containing a compound that increases cellular ceramide levels is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) 25 value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The above-described assay will be referred to herein as the "Golden Syrian hamster" assay. Preferred compositions provide a reduction in hair growth 30 of at least about 15%, more preferably at least about 25%, and most preferably at least about 35% when tested in the Golden Syrian hamster assay. Compositions described in Examples 1 and 2 (above) were tested in the Golden Syrian hamster

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assay; the results are provided in Table 1:

Table 1

Reduction of Hair Mass					
	Compound	Weight %	% Reduction	Left (mg)	Right (mg)
5	PDMP	10	40 ± 11	0.99 ± .11	1.83 ± .20
	PPMP	2.5	32 ± 14	1.60 ± .44	2.37 ± .66
	PPPP	1	42 ± 13	0.95 ± .31	1.80 ± .49
10	(1S,2R)-(+)-Phenyl propanolamine	10	40 ± 6	1.72 ± .27	2.96 ± .46
	N-Oleylethanolamine	10	48 ± 6	1.00 ± .11	1.99 ± .16
	C <sub>8</sub> -Ceramide	1	17 ± 12	1.18 ± .17	1.49 ± .12
	C <sub>8</sub> -Ceramide	3	30 ± 5	1.53 ± .16	2.23 ± .28
	C <sub>6</sub> -Ceramide	2.5	40 ± 7	1.99 ± .39	3.17 ± .39
15	C <sub>2</sub> -Ceramide	1	16 ± 7	1.67 ± .18	2.14 ± .33
	C <sub>2</sub> -Ceramide	3	42 ± 7	1.85 ± .34	3.10 ± .36

Glucosylceramide Transferase Assay

This assay has been previously described generally by Matsuo et al., *Bochimica et Biophysica Acta*, 1116:97-103, 1992. The assay measures the transfer of glucose from <sup>3</sup>H-UDP-glucose to ceramide-silica-60 substrate in the presence of flank organ-derived, hair follicle tissue homogenates. The solid ceramide substrate was prepared by dissolving ceramide in chloroform and adding silica-60 to give a concentration of 20 mg ceramide / mg silica. The chloroform was evaporated under N<sub>2</sub> gas and the silica-ceramide was allowed to dry completely before use in the assay. Each reaction mixture in the assay contained 10 mg of the solid ceramide substrate, 50 µl of hair follicle extract from hamster flank organ, 100 µl <sup>3</sup>H-UDP-glucose (0.54 mM), 250 µl MOPS buffer (25 mM, pH 6.5) containing 1 mM MgCl<sub>2</sub>, 2 mM MnCl<sub>2</sub>, 0.5 mM NADH, and either 600 µl H<sub>2</sub>O or 600 µl H<sub>2</sub>O containing a compound that is an inhibitor of glucosylceramide transferase.

Reactions were initiated with the addition of the radiolabeled glucose and incubated at 37°C with gentle rocking. Background was determined using silica-60 without ceramide. Reaction mixtures were microcentrifuged and the silica-ceramide was

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washed 3 times with 1 ml phosphate buffer saline (PBS) and analyzed using liquid scintillation.

The assay conditions were optimized for time, protein concentration and ceramide substrate concentration. The catalytic activity of the enzyme was 5 found to be linear with time over a 20 minute incubation period at 37°C. Linearity with respect to protein concentration was shown to range from 10 micrograms/mL up to 75 micrograms/mL. Also, glucosylceramide synthase activity was linear with respect to ceramide substrate concentration in the range from 5  $\mu$ g/mL up through 50  $\mu$ g/mL with enzyme activity ranging from 625 - 850 pmoles/minute x mg 10 protein.

The hair follicle extracts were found to possess glucosylceramide synthase activity. Several known inhibitors of glucosylceramide synthase (PDMP, PPMP and PPPP) that were demonstrated to reduce hair mass were also shown to inhibit flank organ-derived hair follicle glucosylceramide synthase activity, *in vitro* 15 (Table 2). In general, the enzyme inhibition is dependent on the concentration of the inhibitor used, such that increasing the inhibitor dose results in increased inhibition of the enzyme.

Table 2			
Inhibition of hair follicle glucosylceramide synthase activity			
<u>Inhibitor</u>	<u>Control Activity Without Inhibitor</u>	<u>Activity with Inhibitor Present</u>	<u>Percent Inhibition</u>
(pmoles $^3$ H-glucose incorporated/min x mg protein)			
PDMP 0.5 mM	177 $\pm$ 15	15 $\pm$ 10	92 $\pm$ 6
PPMP 0.5 mM	173 $\pm$ 15	46 $\pm$ 11	73 $\pm$ 6
PPPP 0.5 mM	190 $\pm$ 16	149 $\pm$ 31	22 $\pm$ 9

Generally, preferred inhibitors of glucosylceramide synthase inhibited hair follicle glucosylceramide synthase activity by at least 20% and preferably by 50% when tested in the assay described above using the 0.5 mM concentration of 30 the inhibitor used to generate the test results in Table 2.

An analogous assay can also be used to test inhibitors of ceramidase

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for their inhibiting affect on hair follicle ceramidase activity.

Ceramidase activity can be measured by incubating 40 mM of a buffer containing 0.21 M sucrose, 0.8 mM EDTA, 4 mg/ml deoxycholate, 0.7 mg/ml Triton X-100, 0.62 mM [<sup>3</sup>H] ceramide and 0.1-0.5 mg protein. The 5 compound to be tested for ceramidase inhibition can be added at 0.5 mM. Reactions are then incubated at 37°C for 60 minutes and the reactions are stopped by the additions of 100  $\mu$ l palmitic acid and 4 ml 10% citric acid and 5 ml hexane. The tubes are mixed and centrifuged and the hexane phase transferred to a clean tube and the aqueous phase re-extracted with an additional 5 ml hexane. The 10 hexane extracts are combined and dried under nitrogen. The residue is dissolved in 100  $\mu$ l chloroform and a 4  $\mu$ l aliquot is removed for analysis by liquid scintillation. A 16  $\mu$ l aliquot is applied to a lane on a thin layer plate, which is then developed with hexane; ethyl ether; acetic acid (70:30:1). The release of free fatty acid is determined by radiochemical analysis to indicate ceramidase activity. See generally, 15 Wertz, P.W. and Downing, D., "Ceramidase activity in porcine epidermis", FEBS 268 (1):110-112, 1990. Generally, preferred inhibitors of ceramidase would inhibit hair follicle ceramidase activity by at least 20% and preferably at least 50% when tested in the above assay.

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C L A I M S

1. A method of reducing mammalian hair growth which comprises:  
selecting an area of skin from which reduced hair growth is desired;  
and
- 5 applying to said area of skin a dermatologically acceptable  
composition comprising a compound that increases cellular ceramide levels in an  
amount effective to reduce hair growth.
2. The method of claim 1, wherein the concentration of said compound  
in said composition is between 0.1% and 30%.
- 10 3. The method of claim 1, wherein the compound provides a reduction  
in hair growth of at least 15% when tested in the Golden Syrian Hamster assay.
4. The method of claim 1, wherein the compound provides a reduction  
in hair growth of at least 25% when tested in the Golden Syrian Hamster assay.
5. The method of claim 1, wherein the compound is applied to the skin  
15 in an amount of from 10 to 3000 micrograms of said compound per square  
centimeter of skin.
6. The method of claim 1, wherein said mammal is a human.
7. The method of claim 6, wherein said area of skin is on the face of  
the human.
- 20 8. The method of claim 6, wherein the composition is applied to the  
area of skin in conjunction with shaving.
9. The method of claim 6, wherein said area of skin is on a leg of the  
human.
10. The method of claim 6, wherein said area of skin is on an arm of the  
25 human.
11. The method of claim 6, wherein said area of skin is in an armpit of  
the human.
12. The method of claim 6, wherein said area of skin is on the torso of  
the human.
- 30 13. The method of claim 1, wherein the composition is applied to an area  
of skin of a woman suffering from hirsutism.
14. The method of claim 1, wherein said hair growth comprises androgen

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stimulated hair growth.

15. The method of claim 1, wherein the composition further includes a second compound that also causes a reduction in hair growth.

16. A method of reducing mammalian hair growth, which comprises:

5 selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising an inhibitor of glucosylceramide synthase in an amount effective to reduce hair growth.

10 17. The method of claim 16, wherein the inhibitor is 1-phenyl-2-decanoyle-amino-3-morpholino-1-propanol.

18. The method of claim 16, wherein the inhibitor is 1-phenyl-2-hexadecanoyle-amino-3-morpholino-1-propanol.

19. The method of claim 16, wherein the inhibitor is 1-phenyl-2-hexadecanoyle-amino-3-pyrrolidino-1-propanol.

20. The method of claim 16, wherein the inhibitor is 1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol.

21. The method of claim 16, wherein the inhibitor is D-threo-4'-hydroxy-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol.

20 22. The method of claim 16, wherein the inhibitor is D-threo-3',4'-methylenedioxypheyl-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol.

23. The method of claim 16, wherein the inhibitor is D-threo-trimethylenedioxypheyl-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol.

24. The method of claim 16, wherein the inhibitor is

25 D-threo-3',4'-ethylenedioxypheyl-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol.

25. The method of claim 16, wherein the inhibitor is N-butyldeoxy-nojirimycin (NBDN).

26. The method of claim 16, wherein the inhibitor is N-(5-adamantane)-1-yl-methoxy)pentyl)-deoxy norjirimycin.

27. The method of claim 16, wherein the inhibitor inhibits glucosylceramide synthase activity in hair follicles by at least 20%.

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28. The method of claim 16, wherein the inhibitor inhibits glucosylceramide synthase activity in hair follicles by at least 50%.
29. A method of reducing mammalian hair growth, which comprises: selecting an area of skin from which reduced hair growth is desired;  
5 and applying to said area of skin a dermatologically acceptable composition comprising an inhibitor of ceramidase in an amount effective to reduce hair growth.
30. The method of claim 29, wherein the inhibitor is D-erythro-2-(N-myristoylamino)-1-phenyl-1-propanol.
- 10 31. The method of claim 29, wherein the inhibitor is N-oleoyl ethanolamine.
32. The method of claim 29, wherein the inhibitor is (1S,2R)-(+)-phenylpropanolamine.
- 15 33. A method of reducing mammalian hair growth, which comprises: selecting an area of skin from which reduced hair growth is desired; and applying to said area of skin a dermatologically acceptable composition comprising ceramide or a ceramide analog.
- 20 34. The method of claim 33, wherein the composition includes ceramide.
35. The method of claim 33, wherein the composition includes N-hexanoylsphingosine.
36. The method of claim 33, wherein the composition includes N-octanoylsphingosine.
- 25 37. The method of claim 33, wherein the composition includes N-octanoyl-DL-erythro dihydrosphingosine.
38. The method of claim 33, wherein the composition includes N-octyl-D-erythro-sphingosine.
39. The method of claim 33, wherein the composition includes  
30 N-thioacetylsphingosine.
40. The method of claim 33, wherein the composition includes 4-dodecanoylamino-decan-5-ol.

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41. The method of claim 33, wherein the inhibitor inhibits ceramidase activity in hair follicles by at least 20%.

42. The method of claim 33, wherein the inhibitor inhibits ceramidase activity in hair follicles by at least 50%.

5 43. A method of reducing mammalian hair growth, which comprises: selecting an area of skin from which reduced hair growth is desired; and applying to said area of skin a dermatologically acceptable composition comprising an inducer of sphingomylinase in an amount effective to 10 reduce hair growth.

44. A method according to any one of claims 1 to 43, wherein said applying of said composition has a cosmetic effect.

45. The use of a compound which is (1) an inhibitor of glucosylceramide synthase, (2) an inhibitor of ceramidase; (3) ceramide; (4) a ceramide analog; and/or 15 (5) an inducer of spingomylinase; for the manufacture of a medicament for inhibiting mammalian hair growth.

46. The use according to claim 45, wherein said compound is as defined in any one of claims 17-26, 30-32 or 35-40.

47. A method of producing a composition for inhibiting mammalian hair 20 growth, which comprises selecting a compound which is (1) an inhibitor of glucosylceramide synthase, (2) an inhibitor of ceramidase; (3) ceramide; (4) a ceramide analog; and/or (5) an inducer of spingomylinase; and combining said compound, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.

25 48. A method according to claim 47, wherein said vehicle or carrier is adapted to be spread upon the skin of a mammal.

49. A method according to claim 47 or 48, wherein a cosmetic composition is produced.

50. A method according to claim 47, 48 or 49, wherein said compound is 30 as defined in any one of claims 17-26, 30-32 or 35-40.

51. The new use of a compound which is (1) an inhibitor of glucosylceramide synthase, (2) an inhibitor of ceramidase; (3) ceramide; (4) a

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ceramide analog; and/or (5) an inducer of spingomylinase; for reducing hair growth.

52. A composition when used for inhibiting mammalian hair growth, which includes a compound which is (1) an inhibitor of glucosylceramide synthase, (2) an inhibitor of ceramidase; (3) ceramide; (4) a ceramide analog; and/or (5) an inducer of spingomylinase; in an amount effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

53. A composition according to claim 52, wherein said compound is as defined in any one of claims 17-26, 30-32 or 35-40.

54. A composition according to claim 52 or 53, which is a cosmetic composition.

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